THE
AMERICAN NATURALIST

Vol. XCV September–October, 1961 No. 884

SOME PARALLELS BETWEEN GENE CONTROL SYSTEMS IN MAIZE AND IN BACTERIA

BARBARA McCLINTOCK

Department of Genetics, Carnegie Institution of Washington,
Cold Spring Harbor, New York

It has been realized for some time that, although the gene is necessary for expression of a certain phenotype, it may not in itself be sufficient for such expression and mechanisms may exist that control its action. Genetic systems that serve this purpose in maize were recognized some years ago, and studies conducted with a number of them have been reported (for references, see Brink, 1958, 1960; McClintock, 1956a and b; Peterson, 1960). Without adequate confirmation of similar systems in other organisms, it could be considered that the systems in maize may not reflect a type of control of gene action that is common to organisms in general. Recently, however, genetic systems that control gene action have been discovered in bacteria (Jacob and Monod, 1959, 1961; Jacob *et al.*, 1960) and it is now apparent that a relationship may exist between the bacterial and the maize control systems. The bacterial control systems, described by Jacob *et al.*, are composed of two genetic elements, each distinct from the "structural" gene. One of them, designated the "operator," is located adjacent to the structural gene (or sequence of structural genes) and controls its activation. The structural gene, when activated, is responsible for the production of a particular sequence of amino acids and thus for the specificity of a protein. The second element of this system, termed the "regulator," may be located close to the structural gene, or it may be located elsewhere in the bacterial chromosome. The regulator is responsible for the production of a repressor substance—not a protein—that appears in the cytoplasm. The operator element responds in some yet unknown manner to changes in degree of effective action of the repressor substance by "turning on" or "turning off" the action of the structural gene in accordance with such changes. Each operator-regulator system is specific, in that an operator will respond only to the specific product of the regulator of its system.

In maize likewise, some of the control systems are composed, basically, of two elements. One is closely associated with the structural gene and directly controls its action; it may be likened to the operator element in bacteria. The other element may be located near the first or may be independently located in the chromosome complement. It establishes the conditions

to which the gene-associated element responds, a particular change in these conditions being reflected in a particular change in action of the gene, and thus is comparable to the regulator element in bacteria. In maize, as in bacteria, each "operator-regulator" system is quite specific: an "operator" element will respond only to the particular "regulator" element of its own system.

Several different two-element control systems, each operating independently of the others, have been identified in maize. These were discovered, originally, because the elements belonging to each were transposed from one location to another in the chromosome complement without losing their individual identities in the process. It was found that the gene-associated element of a system can leave the locus of one gene and become associated with that of another. After such an association is established, the action of the gene comes under the control of the system to which the gene-associated element belongs. It has been possible, therefore, to examine the mode of operation of a particular control system at a number of different gene loci and, conversely, to examine the operation of different control systems at the same gene locus. It should be emphasized that, although transposition of controlling elements in maize made it possible to recognize their presence in the chromosome complement and to study the mode of operation of the component elements of a system, transposition does not necessarily characterize the behavior of a controlling element. An element previously exhibiting transposition may become fixed in location. If it is the gene-associated element that becomes fixed, the action of the gene will then be permanently under the control of the system to which that element belongs. Examples will be considered in this report.

Jacob (Jacob, 1960; Jacob, Schaeffer and Wollman, 1960) and Richter (1961) have postulated that controlling elements in maize may be comparable to episomes in bacteria. Recent evidence (Buttin, Jacob and Monod, 1960; Yarmolinsky and Wiesmeyer, 1960) about the manner in which a phage particle may control the action of bacterial genes in the neighborhood of its attachment to the bacterial chromosome lends support to this interpretation. In a lysogenic bacterium, induction of phage by ultraviolet light or by chemical treatment releases inhibition of gene action not only in phage genes that are concerned with initiating vegetative replication but also in genes of the bacterial chromosome in the neighborhood of phage attachment. This effect resembles that which occurs in maize when a controlling element at the locus of a gene is removed by the transposition mechanism. A change in action of the gene accompanies this removal.

Notwithstanding the analogies that may be drawn between controlling elements in maize and episomes in bacteria, it now appears to the author that control systems in maize also resemble the operator-regulator systems of control of gene action in bacteria, as outlined above. In maize, as in bacteria, the controlling element (the "operator") at the locus of the structural gene responds to altered activities of the second element (the "regulator") of the system by inducing modification in action of the structural gene. In

maize, the response of the "operator" element to change in effective action of the "regulator" element results in controlled types of change in action of the structural gene, and many such changes are accompanied by removal of the "operator" element from the locus. In other cases, however, the "operator" element is not removed from the locus. It responds merely by "turning on" or "turning off" the action of the structural gene. When this occurs, the maize systems resemble the operator-regulator systems in bacteria.

The control system composed of the elements Dissociation (*Ds*) and Activator (*Ac*) was the first of those in maize to be explored extensively. Its mode of operation was examined at a number of different gene loci (McClintock, 1953). This system was studied intensively because it was possible to identify readily both the "operator" element, *Ds*, and the "regulator" element, *Ac*. In several cases (bz^{m-4}, sh^{m}, c^{m-1}) the proximal or distal position of *Ds* with respect to the components of the structural gene could also be determined. With some other two element systems, the regulator element is readily identifiable but the presence of the operator element at the gene locus often must be assumed on the basis of the control that the regulator exerts on gene action. However, when adequate test methods are available, it is possible to confirm the presence of an operator element at the locus of the gene by means of crossover techniques which are capable of defining its location with respect to the components of the structural gene. This method has been used successfully to define the location of this element in the case where action of the structural gene, A_1, came under the control of the two-element system of which Dotted (*Dt*) is the regulator (Laughnan, 1955; Sarma, 1956, 1961).

This report will describe the mode of operation of the elements that compose a single control system in maize. It is not the purpose of the paper to present the evidence for the statements that will be made here but rather to indicate some of the resemblances between the systems in bacteria and those in maize. The Suppressor-mutator control system in maize has been chosen because it illustrates these resemblances more directly than do other examined systems in maize.

Five independent inceptions of control of gene action by the Suppressor-mutator (*Spm*) control system have been recognized in the Cold Spring Harbor cultures. Three of them occurred when the "operator" element of this system was inserted at the locus of A_1 in chromosome 3. These three cases are designated $a_1{}^{m-1}$, $a_1{}^{m-2}$, and $a_1{}^{m-5}$. The symbols m-1, m-2, and m-5 refer to the order in time of inception of control of gene action at A_1 by this system ($a_1{}^{m-3}$ and $a_1{}^{m-4}$ refer to inceptions of control of gene action at A_1 by the *Ds-Ac* control system). A fourth case occurred at the A_2 locus in chromosome 5 (designated $a_2{}^{m-1}$), and a fifth at the *Wx* locus in chromosome 9 (designated wx^{m-8}). (Both A_1 and A_2 are associated with anthocyanin pigment formation in plant and kernel. *Wx* is associated with production amylose in the pollen grain and in the endosperm of the kernel.) Two independently located elements are primarily responsible for control of gene action at $a_1{}^{m-1}$, $a_1{}^{m-5}$, $a_2{}^{m-1}$, and wx^{m-8}. One controlling element, com-

parable to the operator, resides at the locus of the gene and directly controls its type of action. The other element, comparable to the regulator, is *Spm*, to which the "operator" element at the locus of the gene responds in accordance with the type of activity of *Spm* and the changes in this activity. Preliminary evidence suggests that *Spm* resides close to the A_1 locus in the case of $a_1{}^{m-2}$. It is possible that here the "operator" and "regulator" elements of the system are located adjacent or close to each other. If this proves to be true, $a_1{}^{m-2}$ will resemble in its organization and its behavior one of the cases examined in studies of the *Ds-Ac* system. (See discussion of bz^{m-2} in McClintock, 1956c.)

Basically, the mode of control of gene action by the *Spm* system is relatively easy to comprehend. However, there are some conditions that complicate its analysis and so obscure its basic simplicity. They arise from (1) alterations at the locus of the gene (termed "altered states" of the gene locus), induced by the controlling element there residing, that modify subsequent expression of the gene, both in the presence and in the absence of *Spm*; (2) modifications of *Spm* itself, expressed by altered degrees in strength of its action, or by cyclically occurring change in phase of its activity—from active to inactive and back to active; and (3) the action of an independently located, transposible Modifier element that alters the expression of some of the states of the gene locus in a predictable manner, but only when *Spm* is also present and in its active phase. Each of these conditions will be considered in turn. The discussion will apply to those cases in which the two elements that are basically concerned in control of gene action are independently located, one being at the locus of the gene, the other, *Spm*, being located elsewhere.

THE CLASS I AND CLASS II STATES OF A GENE LOCUS UNDER THE CONTROL OF THE *Spm* SYSTEM

There are two main categories of state, designated class I and class II. Because the class II states behave in a simple manner, they will be considered first. In the presence of a fully active *Spm*, no gene action is expressed. If *Spm* is removed by somatic transposition, or by meiotic segregation, or if it enters its inactive phase in a cell of the plant or the kernel, gene action is expressed. The degree of expression serves to distinguish between different members of the class II states. An apparently full, or near full gene expression characterizes some class II states whereas a much reduced expression characterizes others. With the class II states, *Spm* serves as the "regulator" of action of the "structural" gene, causing it to be "turned on" and "turned off" through the direct mediation of the "operator" element residing at the locus of the "structural" gene. It should be emphasized that this turning on and turning off of gene action is not accompanied by any modification that permanently alters the structure of the gene locus, as may occur with the class I states. However, the class II states originate from the class I states, which will now be described.

Because of the variety of expressions that may be produced by class I states, they appear to be far more complex than the class II states. Regardless of the degrees of difference in expression, all class I states exhibit the same basic pattern of behavior. With respect to any one gene under the control of the *Spm* system, all the many different class I states that have been isolated trace their origin to the class I state that was produced, initially, when the "operator" element became associated with the structural gene. Each class I state is distinguished not only by its behavior pattern in the presence of active *Spm*, but also by the type of gene action that it gives rise to in the absence of *Spm* (or in the presence of *Spm* in an inactive phase). When a fully active *Spm* is present, all gene action is suppressed until, in a cell of the plant or of the kernel, a modification is instigated at the locus of the gene by the "operator" element there residing. Each class I state is distinguished by a particular type of consequence of such modifications. There are two main consequences: production of a mutant, which is thereafter stable in the presence of active *Spm*; or production of a new state, either class I or class II. The time during development of a plant or kernel when these modifications occur, the number of cells in which they occur at any one stage in development, and the particular types of consequence, serve to characterize a particular class I state. For example, with some states, such modifications at the locus of the gene may occur early in development, but each state is distinguished from others by the type of consequence of these modifications. One such state may give rise to two main types of stable mutants, those that express high levels of gene action and those that give the null expression; and these two types of mutants are produced at constant relative rates. With another such state, the early-occurring mutations result only in mutants that express low levels of gene action. Some class I states give rise to many new states whereas others produce few new states.

There is a group of class I states characterized by the fact that all mutation-inducing events occur late in development of plant or kernel. The states in this group may be distinguished from one another by differences in the number of phenotypically distinguishable mutant areas that are produced, and also by the levels of gene action these mutant areas exhibit. These states are particularly useful for many studies. Mutation-inducing events occur so late in development that germinal mutations may not be encountered or are encountered only rarely. Thus, such states are preserved, unaltered, through generations of plants, even when *Spm* is present and fully active in the plants.

In the absence of *Spm* all but one of the many class I states that have been isolated express some degree of gene action. The level of action may be low with some states, intermediate with others, and even quite high with still others. As long as *Spm* is absent (or is present in its inactive phase), the particular type of gene action expressed by any one state is constant and may be maintained unaltered from generation to generation. Also, in the

absence of an active *Spm*, any state behaves as a stable allele of any other state. However, no relation has been observed between the type of gene expression that a class I state exhibits in the absence of *Spm* and the types of mutation it produces in its presence.

If, in a plant having an active *Spm*, a different class I state is carried in each homologue, each state reacts to *Spm* in its own individual manner, and each may be recovered in the progeny, unaltered by its association in the same nucleus with the other state. Again, if two different gene loci, each under the control of the *Spm* system, are present in a plant or a kernel—for example, a_2^{m-1} and wx^{m-8}—each responds to *Spm* in its own characteristic manner according to its state. It may be added, also, that in plants or kernels having two such states each state responds directly to a somatically occurring change in action of *Spm*. Each depicts this change in the expected manner, in accordance with its state (see below).

TYPES OF CHANGE IN *Spm*

Spm itself undergoes modification. After a modification has occurred, the *Spm* exhibiting it may be isolated and further examined. The modifications may result in one of several different types of change in *Spm* action or behavior. One type affects the time during development of the plant when transposition of *Spm* will occur. Some isolates of *Spm* undergo transposition mainly early in development. Others undergo transposition mainly late in development, with only an occasional occurrence in young tissues. Several isolates have been obtained that rarely undergo transposition at times during development that will result in the appearance of gametes in which *Spm* occupies a new location in the chromosome complement; and one isolate has not yet given any evidence of transposition.

One conspicuous type of change undergone by *Spm* results in a weakening of its capacity to effect mutation with the class I states of those gene loci that have come under the control of the *Spm* system. The designation Spm^w is used to symbolize this type of alteration of *Spm* (McClintock, 1957). In this section, the symbol Spm^s will henceforth be used to designate an *Spm* expressing full activity. A newly arising Spm^w may be recognized readily. With the class I states, its presence is made evident by a pronounced delay in time of occurrence of mutation at the locus of the gene, and also in a pronounced reduction in frequency of occurrence of such mutation. If the class I state is one that gives only late-occurring mutations with Spm^s, then with Spm^w only a few very late-occurring mutations will be produced, and sometimes none at all. If the class I state is one that gives many early-occurring mutations with Spm^s, then Spm^w will delay the time of occurrence of mutation until the late stages of development of a tissue. Only small areas exhibiting the mutant phenotype will appear in plant and kernel. The response of any one class I state to any one isolate of Spm^w is quite predictable.

Each Spm^w arises from an Spm^s as the consequence of a single event occurring within a cell. If it takes place early in plant development, all the

cells producing an ear of the plant may be descendants of the cell in which it occurred, and thus all carry the newly produced *Spm*^{w}. Or, the descendent cells may contribute only to a part of the ear, and the newly produced *Spm*^{w} be evident only in the kernels within a sector derived from these cells. In either case, the *Spm*^{w} may be isolated from those kernels that carry it. There are different types of *Spm*^{w}, distinguishable from each other by several criteria. They differ in degree of weakening of the capacity to induce mutation at the loci of genes controlled by the *Spm* system, in frequency of occurrence of transposition and the time of its occurrence during development, and in stability of the *Spm*^{w} expression. In the last-named respect, differences between *Spm*^{w} isolates of independent origin are conspicuous. Some isolates are highly stable whereas others undergo frequent return to *Spm*^{s}. It is again evident that change in action of *Spm*, this time from *Spm*^{w} to *Spm*^{s}, is effected by a single event occurring in an individual cell.

If both an *Spm*^{w} and an *Spm*^{s} are present in the same plant, *Spm*^{s} is dominant. However, the *Spm*^{w} in such plants may be recovered in their progeny, with its type of action unaltered by previous association in the same nucleus with *Spm*^{s}.

It should be emphasized that no modifications resulting in mutation or change in state will occur at the locus of a gene that is under the control of the *Spm* system (that is, with the class I states of the gene locus), unless all gene action has first been suppressed by *Spm* in the ancestor cells, whether by *Spm*^{w} or by *Spm*^{s}. In other words, suppression of gene action by *Spm* must precede the mutation-inducing event. This fact is especially well illustrated in plants that have an *Spm* element that is undergoing change in phase of its activity during the development of plant or kernel, as described in the next section.

CYCLICALLY OCCURRING REVERSALS OF PHASE OF ACTIVITY OF *Spm*

One of the most interesting and theoretically important types of expression of *Spm* consists in the sequentially occurring reversals in phase of its activity—from active to inactive and back to active (McClintock, 1958, 1959). Each such change in phase results from an event occurring in an individual cell of the plant or kernel. The effect produced by the change is then exhibited in the descendants of this cell, if either a class I or a class II state of a gene locus under the control of this *Spm* system is also present to register it. Following such a reversal of phase, the duration of the particular phase may be long, continuing unaltered through many cell or even plant generations, or it may be short, reversal occurring again in a number of cells only a relatively few cell generations removed from that which initiated the preceding phase. Control of duration of a particular phase appears to be associated with the event that produces the particular reversal of phase. By selective methods it has been possible to isolate *Spm* displaying either a long duration of an active phase or a long duration of an inactive phase.

The phenotypes appearing in mature plants and kernels as the consequence of phase reversal of *Spm* may be very complex. The degree of complexity depends on the state of a gene locus that is present in the plant or kernel, on the number of reversals of phase of *Spm* that occur, and also on the times of their occurrence during development of a tissue. If an inactive *Spm* is present, initially, in a plant or kernel, along with either a class I or a class II state of a gene locus, no evidence of the presence of this *Spm* will appear in either the plant or the kernel unless reversal of phase occurs in one or more cells during development. After *Spm* is reactivated in an individual cell, its presence is revealed in the descendants of that cell. When a class II state is used as the indicator, reactivation of *Spm* is made evident by suppression of gene action in these cells. Should subsequent reversal of phase occur in some of the descendent cells, then gene action will be evidenced in their descendent cells. With the class II states, then, reversals of phase of activity of *Spm* merely effect a "turning on" and "turning off" of gene action; and with the class II states of those gene loci that are associated with the production of anthocyanin pigment, both in plant and in kernel, the alternating cycles of phase of activity of *Spm* are registered with great clarity. No pigment appears in cells in which *Spm* is in its active phase, and pigment appears in those cells in which it is in its inactive phase. It may be pointed out here that the type of control of gene action, just described, resembles that associated with phase variation in Salmonella in which the system of chromosomal elements responsible for control of gene action likewise has been identified (Lederberg and Iino, 1956; Iino and Lederberg, 1957, 1958; Iino, 1959, 1960).

The response of the class I states to reversal of phase of activity of *Spm* is basically the same as that of the class II states, but the types of phenotypic expression of the gene and the various different patterns of expression that may appear in an individual plant or kernel can be very complex. This is because mutation-inducing events may occur at the gene locus in some cells when their *Spm* is in its active phase. The pattern of mutant areas that may appear in a sector of the plant or kernel, after a change in phase of *Spm* from inactive to active, will depend upon the developmental stage of the tissue when the reversal occurs. An example will illustrate this. If a plant or kernel starts development with an active *Spm* having a long duration of the active phase, and also a class I state of the gene locus that responds to it by producing a number of early-occurring mutations, then large areas, each exhibiting a mutant phenotype, will be present in the mature plant or kernel. Each such area reflects an early-occurring "operator"-induced modification at the locus of the gene. If, however, development commences with *Spm* in its inactive phase, no mutations may occur at the gene locus having this class I state unless and until a reversal of phase of activity of *Spm* occurs. If reversal takes place in a cell rather late in the development of a tissue, suppression of gene action will be effected in the descendants of that cell. However, mutation-inducing events may occur in some of these descendent cells and, by necessity, all these mutations will arise in cells

of a tissue that is approaching maturity. Consequently, the areas that can exhibit a mutant phenotype must be small. In other words, the size of the mutant areas will depend upon the stage of development of a tissue when *Spm* reverts to its active phase. It is evident, then, that complex and often irregular patterns of gene expression may be exhibited by a plant or by a kernel carrying a particular class I state when its *Spm* is undergoing frequent reversal of phase of activity. Different patterns of gene expression may be observed in different areas of the same plant or kernel. These patterns reflect the time of occurrence of reversal of phase of activity of *Spm* and also the number of such reversals.

Evidence has been obtained to indicate that inactivation of *Spm*, as described above, is not associated with a complete blocking of its functional capacity but rather with some change affecting its mode of functioning, such as an altered form of its product. This was made evident, initially, in plants and kernels having an inactive *Spm* characterized by a long duration of inactivity, and also an active *Spm* undergoing frequent reversal of phase during development. If only the latter *Spm* were present, a class II state would register each reversal of phase by showing no evidence of gene action in those cells in which it was active and by exhibiting gene action in those cells in which it was inactive. When two active *Spm* elements are present, initially, a class II state registers reversal of phase only when it occurs to both *Spm* elements, either simultaneously in an individual cell, or successively (that is, affecting one *Spm* in one cell and the other *Spm* in a descendant of that cell). Thus, in either plant or kernel, both the number and the size of areas exhibiting gene action will differ according to the number of active *Spm* elements that were present initially. From these patterns, it is often possible to deduce the number of *Spm* elements that are present in a plant or kernel.

It was anticipated that combination of an inactive *Spm*, having a long duration of the inactive phase, with an initially active *Spm* in a plant or kernel carrying a class II state would give rise to a phenotype resembling that produced when only one active *Spm* is present initially. This assumption proved to be incorrect. Instead, it was found that this combination produced a phenotype resembling the one that appears when two active *Spm* elements are initially present in a plant or when three active *Spm* elements are initially present in a kernel. However, the pattern produced by the areas that exhibit gene action (no active *Spm* in them) is much more uniform, and this is particularly well illustrated in the aleurone layer of kernels whose endosperms receive two inactive *Spm* elements from the female parent and one initially active *Spm* from the male parent. All areas exhibiting gene action are small, and they are evenly distributed over the aleurone layer. That this pattern is not produced by reversal of phase of the inactive *Spm*, brought about by association in the same nucleus with an active *Spm*, is made evident when progeny of plants having an initially active *Spm* and the described inactive *Spm* are examined. The inactive *Spm* is recovered with its phase quite unaltered. Also, it appears in the expected proportions of the progeny

in accordance with the type of testcross that has been made to determine this. In order to be certain that the inactive *Spm* appearing in the progeny was the same as that which had been combined with the active *Spm* in the zygote produced from the initial cross, the relative locations of the two *Spm* elements in the chromosome complement had to be known in advance of the initial cross. Also, the location of each had to be determined in the individual progeny.

A number of tests had been made to observe the effects produced on either the class I or the class II states by bringing together in a zygote nucleus, or in a primary endosperm nucleus, an inactive and an active *Spm*. The effects produced in all such tests conformed with that described above. The inactive *Spm* proved not to be totally inactive, although it was quite ineffective by itself. This evidence does not preclude the possibility or the probability that some modifications of *Spm* may result in its total inactivation.

THE MODIFIER ELEMENT IN THE *Spm* SYSTEM

A transposible element that serves to increase the frequency of occurrence of mutation-inducing events with some of the class I states of a_1^{m-1} first appeared in only one of many a_1^{m-1}, *Spm*-carrying kernels on an ear and on only one of several ears produced by an a_1^{m-1}/a_1, *Spm*-carrying plant. This kernel exhibited a marked increase in mutation frequency in comparison with that exhibited by the other a_1^{m-1}, *Spm*-carrying kernels on the ear. The class I state of a_1^{m-1} that was present in the ear-bearing plant was one that undergoes only late-occurring mutations in the presence of an active *Spm*. No change in this state had been observed to occur in many tests conducted with it over a number of plant generations. The presence of a Modifier element, which was responsible for the marked increase in mutation frequency in the exceptional kernel, was revealed in tests conducted with the plant derived from this kernel. Subsequently, the effects produced by this Modifier on the expression of other class I states of a_1^{m-1} were investigated. Study of its effects was confined to a_1^{m-1}, but the results allow the following conclusions to be drawn:

(1) The presence of the Modifier can be detected only when *Spm* also is present in the chromosome complement and only when it is in its active phase. Under these circumstances, the Modifier effects a marked increase in frequency of mutation to stable alleles with some of the class I states, but does not modify the time of occurrence of such mutation. Also, the rate of increase in frequency of mutation is proportional to that produced by the state in the absence of the Modifier. However, if the state is one that produces very many mutations with *Spm* alone, the Modifier does not effect a measurable increase in mutation rate (McClintock, 1958).

(2) When the Modifier is present, the same phenotype is produced with Spm^w as with Spm^s. Thus, plants and kernels that have only Spm^w and the Modifier are not distinguishable in phenotype from those that have Spm^s and the Modifier. However, the presence of either one or the other type of *Spm* may be determined by means of progeny tests. Individuals carrying *Spm* but

no Modifier appear in the progeny, and the type of *Spm* in them is made evident.

(3) The Modifier element is transposible. A number of early-occurring transpositions of it were detected. Its transposition to and away from locations in the chromosome complement close to marked gene loci were examined (McClintock, 1958).

The Modifier element acts as if it could complement both the "regulator" element, *Spm*, and the element of this system that is at the locus of the gene. It complements *Spm* in that in its presence a weakly acting *Spm* (*Spm*^{w}) is as effective as a fully active *Spm* (*Spm*^{s}). It complements the element at the A_1 locus in that in its presence a class I state that gives relatively few mutations with *Spm*^{s} alone can mimic another state that gives many more mutations with *Spm*^{s} alone.

DISCUSSION AND SUMMARY

Although the mode of operation of the *Spm* system of control of gene action, as outlined above, may appear to be complex, it is evident, nevertheless, that the diverse gene expressions that it may produce stem from one basic mechanism of action and response of the component elements of the system. The action of the *Spm* element resembles that of the regulator "gene" in bacteria. It may well be that *Spm* produces a specific repressor substance to which the element of the system at the locus of the gene, the "operator" element, responds by "turning off" gene action. Suppression of gene action requires the presence of this operator element at the locus of the gene. No suppression occurs when an operator element belonging to another system is present at the gene locus, or when the specific operator element of this system is transposed away from the gene locus. In other words, if *Spm* produces a specific repressor substance, then the operator element at the locus of the gene responds only to this specific repressor and to no other. The same principle would apply to all the two-element control systems investigated so far in maize; and in this respect they resemble the two-element control systems in bacteria.

In bacteria, both the operator and the regulator element undergo mutation. The mutations arise from single events, and some of them are reversible. The same applies to the controlling elements in maize. Each can undergo mutation, and each such mutation is produced by a single event. Also, some of them are reversible.

In bacteria, most of the control systems that are subject to analysis effect control of production of specific enzymes in response to certain changes in the cellular environment. A "turning on" and "turning off" of gene action constitute an efficient means of control of production of enzymes in response to changes in intracellular environment. Mutations, such as those that occur with the class I states described above, would effect a differentiation. Some of them could be lethal or could result in competitive disadvantage for unicellular organisms. In higher organisms, such mutations, occurring in somatic tissues, need not be lethal or disadvantageous

and, indeed, may be required. Specific types of mutation occurring at given times during development and produced by a control system, such as the *Spm* system, may effect tissue differentiation along certain paths. However, as emphasized above, the *Spm* system can operate in either way—in a manner similar to that exhibited in bacteria, or in a manner that accomplishes a permanent and specific type of change in gene action.

The class II states of gene loci under the control of the *Spm* system best illustrate the similarities in mode of operation of the bacterial and the maize systems. The "operator" element is fixed in location. No transpositions of it away from the gene locus occur, nor does it effect mutation at the gene locus. Its behavior is much the same as that of the operator "gene" in bacteria. If *Spm* produces a specific repressor substance, then the operator element responds to this by "turning off" gene action. If the repressor substance is not produced, or if its structure is modified by mutations that occur to *Spm*, then gene action is "turned on." A class II state, with its operator element fixed in position and an *Spm* element that also is fixed in position, gives rise to a system of control of gene action in maize that simulates in its mode of operation some of the described systems in bacteria. As stated earlier, cases of effective fixation of *Spm* at a specific locus have been found.

Study of the *Spm* system has shown that a relatively simple system of control of gene action may be derived from one that originally expressed a seemingly complex pattern of such control and it may be no coincidence that this simple system resembles those recently discovered in bacteria and in phage. It is expected that such a basic mechanism of control of gene action will be operative in all organisms. In higher organisms, lack of means of identifying the components of a control system of this type may be responsible for delay in recognition of their general prevalence, even though there is much genetic and cytological evidence to indicate that control systems do exist. It is anticipated, however, that control systems exhibiting more complex levels of integration will be found in the higher organisms.

LITERATURE CITED

Brink, R. A., 1958, Mutable loci and development of the organism. J. Cellular Comp. Physiol. (Suppl. 1): 169–196.

1960, Paramutation and chromosome organization. Quart. Rev. Biol. 35: 120–137.

Buttin, G., F. Jacob and J. Monod, 1960, Synthèse constitutive de galactokinase consécutive au développment des bactériophage λ chez *Escherichia coli* K 12. Compt. rend. 250: 2471–2473.

Jacob, F., 1960, Genetic control of viral function. The Harvey Lectures, Ser. 54: 1–39.

Jacob, F., and J. Monod, 1959, Gènes de structure et gènes de régulation dans la biosynthèse des protéins. Compt. rend. 249: 1282–1284.

1961, Genetic regulatory mechanisms in the synthesis of proteins. J. Mol. Biol. 2: 318–356.

Jacob, F., D. Perrin, C. Sanchez and J. Monod, 1960, L'opéron: groupe de gènes à expression coordonnée par un opérateur. Compt. rend. 250: 1727-1729.

Jacob, F., P. Schaeffer and E. L. Wollman, 1960, Episomic elements in bacteria. Tenth Symp. Soc. Gen. Microbiol.: 67-91.

Iino, T., 1959, Curly flagellar mutants in Salmonella. Natl. Inst. Genet. (Japan) Ann. Rept. 9: 95.

1960, Unequal recombination in Salmonella. Natl. Inst. Genet. (Japan) Ann. Rept. 10: 112-113.

Iino, T., and J. Lederberg, 1957a, Transductional analysis of phase variation in Salmonella. Natl. Inst. Genet. (Japan) Ann. Rept. 7: 89-91.

1957b, An analysis of monophase variation in Salmonella. Genetics 42: 378.

1958, Transductional analysis of monophasic types of Salmonella. Natl. Inst. Genet. (Japan) Ann. Rept. 8: 101-102.

Laughnan, J. R., 1955, Structural and functional bases for the action of the A alleles in maize. Am. Naturalist 89: 91-103.

Lederberg, J., and T. Iino, 1956, Phase variation in Salmonella. Genetics 41: 743-757.

McClintock, B., 1953, Induction of instability at selected loci in maize. Genetics 38: 579-599.

1956a, Intranuclear systems controlling gene action and mutation. Brookhaven Symp. Biol. 8: 58-74.

1956b, Controlling elements and the gene. Cold Spring Harbor Symp. Quant. Biol. 21: 197-216.

1956c, Mutation in maize. Carnegie Inst. Wash. Yrb. No. 55: 323-332.

1957, Genetic and cytological studies of maize. Carnegie Inst. Wash. Yrb. No. 56: 393-401.

1958, The Suppressor-mutator system of control of gene action in maize. Carnegie Inst. Wash. Yrb. No. 57: 415-429.

1959, Genetic and cytological studies of maize. Carnegie Inst. Wash. Yrb. No. 58: 452-456.

Peterson, P. A., 1960, The pale green mutable system in maize. Genetics 45: 115-133.

Richter, A., 1961, Attachment of wild type F factor to a specific chromosomal region in a variant strain of *Escherichia coli* K 12: The phenomenon of episomic alternation. Genet. Res. 2 (in press).

Sarma, M. S., 1959, A test of the mutational hypothesis for the origin of the noncrossover alpha derivatives from A^b:P and A^b:Ec. Maize Genet. Cooperation News Letter 33: 44-48.

1961, Colorless components of the A^b:Ec and A^b:P complexes in maize. Maize Genet. Cooperation News Letter 35: 47-50.

Yarmolinsky, M. B., and H. Wiesmeyer, 1960, Regulation of coliphage *lambda* of the expression of the capacity to synthesize a sequence of host enzymes. Proc. Natl. Acad. Sci. U.S. 46: 1626-1645.